CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

IMIPROTHRIN

Chemical Code # 5327, Tolerance # 52421

March 3, 1999

I. DATA GAP STATUS

Combined, rat:	No data gap; No adverse effect
Chronic toxicity, dog:	No data gap; Possible adverse effect
Oncogenicity, mouse:	No data gap; No adverse effect
Reproduction, rat:	No data gap; No adverse effect
Teratology, rat:	No data gap; No adverse effect
Teratology, rabbit:	No data gap; No adverse effect
Gene mutation:	No data gap; No adverse effect
Chromosome effects:	No data gap; Possible adverse effect
DNA damage:	No data gap; No adverse effect
Neurotoxicity:	No data gap; Possible adverse effect

Toxicology one-liners are attached.

All record numbers through 166057 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T174519
Leung & Kellner, 3/3/99

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 52421-029 160770 "Combined Chronic Toxicity and Oncogenicity Study of S-41311 in Rats" (Nakamura, J. 835-Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan; Study # 500069, 1/27/95). S-41311 technical (lot no. Y-011001, purity 92.9%) was administered in the feed to 50 Sprague-Dawley rats/sex/dose for 104 weeks (main group) and to 14 rats/sex/dose for 52 weeks (satellite group) at levels of 0, 50, 250, 2500 or 5000 ppm. No apparent effects on mortality or clinical signs reported. Body weight gain and food consumption was decreased in 2500 and 5000 ppm males and high-dose females. At 52 weeks, males at 2500 and 5000 ppm had decreased hematocrit values and extended prothrombin time. In females, MCHC increased in the 2500 ppm group. At week 104, MCV was decreased in males at 2500 and 5000 ppm. At 78 weeks (main group), high-dose males showed increased ?-GTP activity, albumin and ß-globulin. In satellite males, enlargement of the liver was noted in one rat at 2500 ppm and 4 rats at 5000 ppm; enlargement of the submandibular gland was seen in 2 high-dose males. At 104 weeks (main group), males at 5000 ppm showed significantly increased pitted foci of the liver. Satellite group males at 2500 and 5000 ppm showed increased relative liver and kidney weights; high-dose males showed increased relative weight of heart and salivary glands (submandibular and sublingual). Absolute weight increases were noted in the liver and salivary glands of high-dose males. Increased incidence of hemosiderosis of the spleen was seen in satellite females at 2500 and 5000 ppm. Increased incidence of ulceration of non-glandular stomach was reported in high-dose males that died or were moribund sacrificed. Relative weights of liver, brain and salivary glands were increased in the high-dose females. In the main group (104 weeks), increased relative salivary gland weight was noted in males at 2500 and 5000 ppm. **No Adverse Effect; Chronic NOEL(M/F)=250 ppm** (males: 8.7 mg/kg/day; females: 10.7 mg/kg/day; based on increased acinar cell hypertrophy of the submandibular gland at 2500 and 5000 ppm). **No Adverse Oncogenic Effects.** Acceptable. Kellner, 9/15/98.

017; 160756; "Three-Month Subacute Toxicity Study of S-41311 by Dietary Administration in Rats" (Adachi, H., Environmental Health Science Laboratory, Sumitomo Chemical Company, Limited, Osaka, Japan, Unique Study Identifier Number 200040, Study No. 2323, 5/19/92). 821. S-41311 (Lot No. Y-011001, purity=92.9%) was admixed to the feed at concentrations of 0, 100, 3000, 6000, or 10000 ppm (0, 5.9, 178.6, 350.4, and 611.2 mg/kg/day, respectively, for males and 0, 6.7, 196.6, 399.0, and 657.0 mg/kg/day, respectively, for females) and fed to 12 Crj:CD(SD) rats per sex per dose level continuously for a period of 13 weeks. No animals died during the study.
A statistically significant decrease in mean body weights was observed in males and females at 6000 and 10000 ppm on Days 34, 56, and 91 with reduced food consumption. Statistically significant decreases in mean hematocrit levels in males and females at 3000, 6000, and 10000 ppm, in mean hemoglobin levels in males at 3000, 6000, and 10000 ppm and in females at 6000

to treatment and were conducted on only 6 animals per sex per dose level at Week 12). (Corlett, 8/13/98)

CHRONIC TOXICITY, DOG

**** 52421-022 160761** "S-41311 Toxicity To Dogs By Repeated Oral Administration For 52 Weeks" (Smith, T. 831-Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England. Study # SMO 398/931098, 6/7/94). S-41311 technical (lot no. Y-011001, purity 92.9%) was administered orally (via capsule) to 4 Beagle dogs/sex/dose at levels of 0, 5, 50, 500 mg/kg/day for 12 months. There was a treatment-related decrease in body weight gain and food consumption in high-dose dogs. Clinical signs in both sexes consisted of increased liquid feces (50 or 500 mg/kg), salivation (500 mg/kg) and vomiting (500 mg/kg). Reduced mean PCV, hemoglobin and RBC counts for both high-dose males and females was noted at week 13 and 39. High-dose males also showed reduction in these values at week 26 and 52. Significantly reduced neutrophil counts in high-dose males were seen at week 26. High-dose dogs showed slightly higher GPT levels at most weeks tested; slightly increased cholesterol, triglyceride and phospholipid values were seen primarily in high-dose males and slightly reduced glucose values were noted in females at this level. Darkening of the liver was reported in all animals at 500 mg/kg and one female at 50 mg/kg/day. A pale, thin margin of the left lateral lobe was also reported in one animal of each sex at 500 mg/kg. Increased liver weights were noted in one dog of each sex at 50 mg/kg and three males and one female at 500 mg/kg. In the gall bladder, prominent mucosal glands were seen in 3 males and 2 females at 500 mg/kg and in 1 female at 50 mg/kg (also seen in one control male). **Possible Adverse Effect**: In the liver, increased centrilobular/portal fibrous tissue was linked to fibrous centrilobular/portal bridging in all high-dose dogs and all females and 3 of 4 males at 50 mg/kg. All high-dose males and 2 of 4 high-dose females showed dilatation of the centrilobular sinusoids. Numbers of pigmented Kupffer cells/macrophages were increased over control in the 50 and 500 mg/kg dose groups. Pigment in centrilobular hepatocytes and incidence of perivascular inflammatory cell infiltration was also increased in these groups. **NOEL(M/F) = 5 mg/kg/day** (based on liver lesions at 50 and 500 mg/kg). Acceptable. Kellner, 9/29/98.

018; 160757; "Three-Month Oral Toxicity Study of S-41311 in Dogs" (Noda, T., Environmental Health Science Laboratory, Sumitomo Chemical Company, Limited, Osaka, Japan, Unique Study Identifier Number 200051, Study No. 2414, 8/27/92). 821. S-41311 (Lot No. Y-011001, purity=92.9%) was administered by means of a gelatin capsule at concentrations of 0, 10, 100, or 1000 mg/kg/day to 4 Beagle dogs per sex per dose level once per day 7 days a week for 91 days [with 2 additional dogs per sex per dose level at the 0 and 1000 mg/kg/day dose levels to test recovery (6 week recovery period used)]. No animals died during the study. Treatment-related watery feces at 100 and 1000 mg/kg/day and salivation at 1000 mg/kg/day in both males and females, and emesis at 1000 mg/kg/day in males were observed. Statistically significant decreases mean red blood cell levels and statistically significant increases in mean platelet counts at 1000 mg/kg/day in both males and females were observed at week 12 (recovery group animals indicate reversibility of these effects). BSP retention test revealed a statistically significant increase in retention rate in both males and females at 1000 mg/kg/day with recovery

;Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan. Study # 2528, 12/19/94). S-41311 technical (lot no. Y-011001, purity 92.9%) was administered in the feed to 51 Crj:CD-1 (ICR) mice/sex/dose at levels of 0, 100, 3500 or 7000 ppm for 78 weeks (main group) or 15 mice/sex/dose for 52 weeks (satellite group). Mortality rates in the 0, 100, 3500 and 7000 ppm main groups were 39.2, 39.2, 39.2 and 46.0%, respectively, in males and 13.7, 19.6, 27.5 and 45.1%, respectively, in females. Body weight gain in both sexes was less than control at 3500 and 7000 ppm; food consumption was decreased in males at 3500 and 7000 ppm and in females at 7000 ppm from week 1; reduction in female food consumption in the 3500 ppm group was noted by week 8. Clinical signs included hair loss in males at 7000 ppm from week 2 and in females at 3500 and 7000 ppm; defect of whiskers was seen in males in the 7000 ppm group from week 4. High-dose males showed decreased RBC count, hemoglobin concentration and hematocrit value and increases in reticulocyte count by week 52. In high-dose females, leucocyte, basophil and lymphocyte counts were increased. Liver weight was increased at 3500 and 7000 ppm (both sexes) at week 52. At terminal sacrifice, liver weight was increased in high-dose males and liver and kidney weights were increased in females at 3500 and 7000 ppm. At 52-week sacrifice, livers showed black discoloration in males at 3500 and 7000 ppm and females at 7000 ppm. At week 78, changes included black discoloration of the liver in males at 3500 and 7000 ppm and females at 7000 ppm. At week 52, increased hepatocyte hypertrophy was noted in both sexes at 3500 and 7000 ppm. **No Adverse Effect**: increased hepatocyte hypertrophy in both sexes at 3500 and 7000 ppm and clear cell foci of the liver in males at 3500 and 7000 ppm (terminal sacrifice); **NOEL =100 ppm** (M=10.2 mg/kg; F= 11.8 mg/kg, based on liver pathology at 3500 and 7000 ppm); slight increase in pulmonary adenocarcinomas in males at 7000 ppm was probably incidental. **No Neoplastic Effects. Acceptable**. Kellner, 8/12/98.

016; 160755; “Preliminary Thirteen-Week Subacute Toxicity Study of S-41311 in Mice” (Adachi, H., Environmental Health Science Laboratory, Sumitomo Chemical Company, Limited, Osaka, Japan, Unique Study Identifier Number 200021, Study No. 2309, 3/10/92). S-41311 (Lot No. Y-011001, purity=92.9%) was admixed to the feed at concentrations of 0, 1000, 3000, 5000, or 7000 ppm (0, 130.1, 370.8, 642.8, and 883.5 mg/kg/day, respectively, for males and 0, 150.4, 435.1, 803.3, and 1239.0 mg/kg/day, respectively, for females) and fed to 12 Crj:CD-1(ICR) mice per sex per dose level for 13 consecutive weeks. No animals died during the study. No treatment-related clinical signs were observed. Statistically significant decreases in mean hematocrit and mean hemoglobin levels in males and females at 3000, 5000, and 7000 ppm were observed and a statistically significant decrease in mean red blood cell levels in males at 5000 and 7000 ppm and in females at 3000, 5000, and 7000 ppm was observed. Statistically significant increases in mean reticulocyte rate and mean reticulocyte count in males at 5000 and 7000 ppm and a statistically significant increase in the mean reticulocyte rate in females at 7000 ppm were observed. A dose-related and statistically significant increase in mean relative liver weights in males and females at all dose levels was observed. Also, a dose-related and statistically significant increase in mean relative spleen weights was observed in males at 5000 and 7000 ppm. Histopathological examination revealed slight extramedullary hematopoiesis in the spleen in males and females at 7000 ppm and slight hypertrophy of hepatocytes in males at 7000 ppm. **No adverse effects**. NOEL (M)< 130.1 mg/kg (1000 ppm) and (F)< 150.4 mg/kg (1000 ppm) (both based on a dose-related increase in mean relative liver weights)

Crl:CD®BR VAF/Plus® rats/sex/dose (F0 mating), with 30 weanlings/sex/dose selected for the F1 mating. F0 and F1 animals were treated for 80 and 84 days prior to mating, respectively, and then during mating, gestation and lactation. There were no treatment-related mortalities, clinical signs or necropsy findings in the F0 and F1 adults. Reduced body weight and food consumption values were noted at 6000 ppm in F0 adults and at 2000 and 6000 ppm in F1 adults. Increased hemosiderosis of the spleen was seen in 2000 and 6000 ppm F0 females, 6000 ppm F0 males and F1 adults. **Paternal NOEL(M/F)=200 ppm** (equivalent in F0 dams: 11.8 to 31.1 mg/kg/day; based on splenic hemosiderosis in F0 females and reduced body weights and food consumption in F1 adults at 2000 and 6000 ppm). In both the F0 and F1 generations, mating parameters (i.e., mating and fertility indices, days cohabitation, gestation, livebirth, viability and lactation indices) were similar to control in all dosage groups. **Reproductive NOEL(M/F)=6000 ppm** (345.8 to 908.8 mg/kg/day; **No adverse effects**). Pup weights were reduced in the 6000 ppm group compared to controls in both generations. **Developmental NOEL(M/F)= 200 ppm** (11.8 to 31.1 mg/kg/day; based on increased rib pairs and 14th rib in day 4 and day 21 culled pups at 2000 and 6000 ppm); **Acceptable**, Kellner, 7/16/98.

TERATOLOGY, RAT

** 52421-024, -025 160763 160764 “Reproduction Study of S-41311 in Rat with Administration during the Period of Fetal Organogenesis” (Ohtsuka, T. 833-Panapharm Laboratory Co., Ltd. Safety Assessment Laboratory, Kumamoto, Japan, Study# 210048, 8/26/92). S-41311 (lot no. Y-011001, purity of 92.9%) was administered via oral gavage (dissolved in corn oil) to 36 pregnant Sprague-Dawley (Crj:CD) rats/dose at levels of 0, 50, 200 or 600 mg/kg/day on days 6 through 17 of gestation. F0 dams (23 or 24 per group) underwent cesarean sectioning on day 20 of gestation; the remaining dams were allowed to deliver naturally. Mature F1 rats were also mated (24, 22, 22 and 16 dams, respectively) and an F2 generation was delivered by cesarean section and examined. Two dose-related deaths occurred in the high-dose group. Tremor and clonic convulsions were noted in almost all high-dose dams soon after dosing (5 min) and about half of these showed prone position and exophthalmos. A smaller number showed staggering gait and incontinentia urinae. The two dams that died showed soiled perinaris, loose stool, salivation, lateral position, hypoactivity and bradypnea. Body weight gain in 600 mg/kg dams was less than control on days 8 to 13 and day 15 of gestation. Reduced body weight gain was also seen at 200 mg/kg and food consumption was reduced at 200 and 600 mg/kg. **Maternal NOEL= 50 mg/kg/ day** (based on reduced weight gain). Reductions in fetal weight and increased fetuses with visceral anomalies and thymic remnant in the neck was seen at 600 mg/kg. Dose-related increases in skeletal variations included lumbar rib (15.67%, 19.82%, 47.51% and 67.95% of fetuses in the 0, 50, 200 and 600 mg/kg groups, respectively), splitting of the vertebral body (0.92%, 0.90%, 2.26% and 13.68%, respectively) and increased pre-sacral vertebra (1.38%, 1.36% and 11.97% in the 0, 200 and 600 mg/kg groups, respectively). Skeletal variations were increased at 200 mg/kg and above. Ossification was decreased in the 5th and 6th sternebrae of 600 mg/kg fetuses. **No Adverse Effects. Developmental NOEL= 50 mg/kg** (based on skeletal variations). **Acceptable**. Kellner, 10/20/98.

of gestation (the day after the first dose) in 2 of 11 high-dose does and extending to day 25 in a single animal. Short-term tremor (lasting about 15 min) was seen soon after administration on day 8 in one 100 mg/kg doe. Body weight gain from day 6 of gestation was less than control in the 100 and 300 mg/kg dose groups and food consumption was significantly reduced in all high-dose does during the treatment period, but recovered to control levels by day 28 of gestation. **Maternal NOEL = 30 mg/kg/day** (based on reduced weight gain). Body weights of fetuses were significantly less than control in the high-dose group, and slightly lower in the 100 mg/kg dose group. Variations in the form of 27 pre-sacral vertebra showed a dose-related trend (1, 6, 7 and 11 fetuses in the control, 30, 100 and 300 mg/kg dose groups, respectively) but the incidence at 30 mg/kg was not significantly different from control, within historical control and not reproduced in a follow-up study. Rib variations (i.e., 13 rib) also showed a slightly increasing incidence with dose (8.1%, 9.3%, 10.0% and 12.5% of fetuses from control to high dose, respectively). A developmental NOEL was not established in the current study; **Developmental NOEL= 30 mg/kg** (based on no fetal effects up to 30 mg/kg in study #160767). **No Adverse Effects. Acceptable**. Kellner, 10/27/98.

GENE MUTATION

** 52421-030 160771 "In vitro gene mutation test of S-41311 in V79 Chinese hamster cells" (Hara, M., 842-Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Study #200046, 8/3/92). S-41311 (lot no. LO-910802B, purity 95.3%) was tested for mutagenic potential in Chinese hamster V79 cells using the HGPRT forward mutation assay with and without metabolic activation (Aroclor 1254-induced rat liver S-9 fraction) in two trials at dose levels of 44.4, 66.7, 100 and 150 µg/ml (without S-9) and 50, 100, 150 and 200 µg/ml (with S-9) in trial 1 and 44.4, 66.7, 100 and 125 µg/ml (without S-9) and 50, 100, 150 and 175 µg/ml (with S-9) in trial 2 (5 hr exposure period). The test compound did not induce any increases in the mutation frequencies as compared with those of the vehicle controls in the presence or absence of S-9 activation. **Acceptable.** Kellner, 8/19/98.

** 52421-030 160772 "Reverse Mutation Test of S-41311 in Bacteria" (Kogiso, S. 842-Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan. Study #200023, 5/6/92). S-41311 technical (lot no. LO-910802B, purity 95.3%) was tested for mutagenic potential in the Salmonella/Mammalian-Microsome Mutagenicity Assay at levels of 0, 156, 313, 625, 1250, 2500 and 5000 ug/plate (triplicate plating) using *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and *E. coli* stain WP-2 uvrA$^-$ with and without metabolic activation (Aroclor 1254-induced rat liver S-9 fraction) in two trials. Cells were preincubated with test material at 37EC for 20 minutes, overlaid onto minimal glucose agar plates and incubated for 65 hours at 37EC. All colony counts in the plate incorporation tests indicated that the test article was negative for mutagenicity. **Acceptable**. Kellner, 8/21/98.

CHROMOSOME EFFECTS

presence of S-9 metabolic activation. **Possible Adverse Effect** (increased structural aberrations, primarily chromatid breaks and exchanges, at 75 and 100 µg/ml and increased polyploid cells at 50 and 75 µg/ml with S-9 metabolic activation). **Acceptable.** Kellner, 8/24/98.

52421-030 160774 “Micronucleus test of S-41311 in mice” (Hara, M. 843-Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan., Study #200041, 4/28/92). S-41311 technical (lot no. LO-910802B, purity 95.3%) was tested for clastogenic activity in polychromatic erythrocytes from bone marrow *in vivo* after 5 CD-1 (ICR) mice/sex/dose were administered the test compound (single i.p. injection) at levels of 0, 19, 38 and 75 mg/kg and sacrificed at 24, 48 and 72 hours; 1000 polychromatic erythrocytes/animal were scored for the presence of micronuclei. Positive control group received cyclophosphamide (40 mg/kg). For the micronucleus test, one mouse of each sex died in the 75 mg/kg dose group; these deaths were probably dose-related. Clinical signs included ataxic gait and urinary incontinence in females at 38 mg/kg. At 75 mg/kg, decreased spontaneous activity, tremor, clonic convulsion, ataxic gait, lateral position and urinary incontinence was noted in males and tremor, clonic convulsion, ataxic gait, prone position and urinary incontinence was seen in females. There were no dose-related increases in the number of micronucleated polychromatic erythrocytes in bone marrow cells compared to control. **No Adverse Effects**. Acceptable. Kellner, 8/26/98.

DNA DAMAGE

** 52421-030 160775 ”*In Vivo/in Vitro* unscheduled DNA Synthesis (UDS) test of S-41311 in rat hepatocytes” (Hara, M., 844; Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan. Study #200045, 7/9/92). S-41311 technical (lot no. LO-910802B, purity 95.3%) was tested for potential DNA damage after administration by oral gavage (dissolved in corn oil) to 3 male Sprague-Dawley rats/dose at levels of 0, 250, 500 or 1000 mg/kg in two separate trials; harvesting of hepatocytes occurred at 3, 12 or 24 hours (trial 1; time-course study) and 3 hours (trial 2; dose response study) after test article administration. Nuclear grains were counted in 100 cells in each of three animals (300 cells/dose). The group means of the net nuclear grain counts for the 3, 12 and 24 hour sampling times were -3.7, -4.4 and -9.8, respectively (Table 1). These values were comparable to the mean control value of -3.2 net grains per nucleus. Net nuclear grains reported after treatment with 250, 500 and 1000 mg/kg S-41311 were -2.7, -3.5 and -2.1, respectively. These values were similar to the control value of -3.1, indicating that S-41311 was negative for DNA damage. **No Adverse Effects**. Acceptable. Kellner, 8/27/98.

NEUROTOXICITY

014, 015; 160753, 160754; “An Acute Study of the Potential Effects of Orally Administered S-41311 on Behavior and Neuromorphology in Rats” (Beyrouty, P., Bio-Research Laboratories Ltd., Senneville, Quebec, Canada, Project No. 97266, 6/22/95). 818. S-41311 (Lot No. Y-011001, purity=88.9%), diluted in corn oil, was administered by gavage in a single dose at concentrations of 0 (corn oil), 100 (females only), 200 (males only), 300 (females only), 600 (males only), and 1000 mg/kg to 12 Sprague-Dawley [Crl:CD®(SD)BR] rats per sex per dose

animal. **Possible adverse effect:** tremors. NOEL (M)=600 mg/kg (based on the presence of tremors during FOB), NOEL (F)=100 mg/kg (based on clinical signs). **Acceptable**. (Corlett, 7/28/98)